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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,363	07/19/2001	Andrew L. Feldhaus	226272003802	5021

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EXAMINER
MOSHER, MARY

ART UNIT	PAPER NUMBER
1648	10

DATE MAILED: 09/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/909,363	Feldhaus
Examiner	**Art Unit**
Mosher	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *7/19/2001, 2/4/2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Double Patenting

Claims 1-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 6,346,415. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims encompass the previously patented subject matter.

Claim Rejections - 35 USC § 112

Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All of the claims involve "a transcriptionally-activated...inverted terminal repeat..less than about 400 bp in length" which exhibits a specified higher level of transcriptional activity compared to a wild-type ITR. Claim 1 (and dependent claims) require a heterologous element, claims 25 and 34 (and dependent claims) specify only a doubling of transcriptional activity without specifying the nature of the alteration in the ITR. A careful reading of the specification indicates that, in all of the working examples, promoter elements are placed 3' to a 146-bp ITR. This is the configuration shown in applicant's figure 1, part E. If the promoter is placed downstream of the A'C'CB'B'A'trs D structure in the working example, how does a "transcriptionally activated inverted terminal repeat" differ from an unmodified ITR adjacent to some small, active promoter? Since the heterologous elements in the working examples are neither repeated or inverted nor enclosed by elements that are inverted and/or repeated, it is not

clear how these embodiments can be considered "inverted terminal repeats". In fact, the AAV p5 promoter increases transcriptional activity compared to the AAV ITR lacking p5 (see Flotte et al, Journal of Biological Chemistry 268:3781-3790, 1993, which states a two-fold increase; see also Wang et al, Gene Therapy 6:667-675, 1999 [not prior art], which states a 10-fold increase). Does a construct with AAV terminal 321-bp meet the limitations of claims 25 and 34, since it is more transcriptionally active than a promoterless wild-type ITR? In conclusion, the metes and bounds are not clear for "a transcriptionally-activated...inverted terminal repeat..less than about 400 bp in length", since the specification seems to define an "activated ITR" as encompassing elements that are not actually included inside an ITR.

In addition, claims 25-27 do not specify that the ITR is an AAV ITR; is AAV intended or is the intent to claim ITRs from other types of viruses (such as retroviruses) ?

Still further, claims 1, 25, and 34 recite "less than about 400 bp in length:, and claims 2 and 26 recite "less than about 200 bp". It is not clear from the specification the range of sizes that can be considered "about 200 bp" or "about 400 bp". For example, it is not clear from the specification whether or not 240 bp or 275 bp would considered "about 200 bp", consequently it is not clear if 234 bp or 263 bp would be considered as "less than about 200 bp". This affects the metes and bounds of the claimed subject matter.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for constructs with a promoter 3' to the ITR, does not reasonably provide enablement for constructs with promoter elements internal to the ITR or 5' to the ITR. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification asserts that a transcriptionally active element can be incorporated 5' to any portion of an ITR (e.g. 5' to the HP region or 5' to the trs) or 3' to any portion of an ITR (e.g. 3' to the B' region of the HP or 3' to the D sequence). However, the ITR region is known to be involved in both priming and cleavage in AAV replication, functions that involve the secondary structures formed by the nucleic acid. At the time the invention was made, very little of the ITR sequence was known to be dispensable (e.g. Wang et al, Journal of Virology 71:3077-3082, 1997; Bohenzky et al, Virology 166:316-327, 1988). The specification discusses placing elements between ITR sequences, or replacing a hairpin with inverted repeats of an element; however, such secondary structure would be likely to interfere with either the ITR function or the transcription function, or both. Therefore one skilled in the art at the time the invention was made would have had reason to doubt assertions that modifications could be successfully made 5' or 3' to any portion within the ITR. The working examples are limited to constructs where modification is located 3' to an intact ITR. Because of the unpredictable effect of modification to ITR biological activity, the state of the art, the scope of the claims, and the limited scope of the working examples, it is concluded that undue experimentation would be required to enable the full scope of the invention, as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-27 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Flotte et al (Journal of Biological Chemistry 268:3781-3790, 1993) or Baudard et al (Human Gene Therapy 7:1309-1322, 1996). In Flotte et al, the pSA313 construct contains 263 bp of AAV terminal sequence containing 145 bp of ITR plus an adjacent transcriptionally activating p5 promoter; this construct is at least two-fold more transcriptionally active than the wild-type 145-base ITR lacking the promoter element. In Baudard et al, the ITR-MDR1 construct contains 234 bp of AAV terminal sequence, including the ITR and adjacent p5 promoter . Because of the indefinite scope of "less than about 200 bp", claim 26 is included in this rejection.

Claims 1, 3, 8-10, 23, 24, 25, 27, 28, 30, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Srivasta 5,252,479. Srivasta contains a working example of a polynucleotide containing 191 bp of AAV ITR adjacent to a 224 bp fragment containing a parvovirus B19 p6 promoter (B19 residues 200-424), see Example 2. This 414-bp construct reasonably meets the vague limitation of "less than about 400 bp", and the B19 p6 promoter is clearly a "heterologous transcriptionally active element". In fact, Srivasta teaches that the promoter fragment contains a promoter-like sequence at B19 nucleotide 320, with transcription likely to originate about 30

bases downstream (column 5, lines 44-51); therefore, the boundaries of Srivasta's "transcriptionally activated ITR" can be reasonably considered to be AAV nt 1-191 + B19 nt 200-350, a length of 341 nt. Therefore the construct reasonably meets a limitation of "less than 400 bp" for the "transcriptionally activated ITR". Since Srivasta does not compare transcription with and without the p6 promoter, Srivasta does not indicate exactly to what extent transcription is increased compared to a promoterless ITR. It is apparent that the construct is transcriptionally active, and it is also apparent that the level of transcription is an inherent property of the construct, regardless of whether or not Srivasta actually compared relative transcription activity. Since the p6 promoter in B19 serves the same function as the p5 promoter in AAV, it is reasonable to assume an improvement comparable to the 2-10-fold improvement observed in ITR-p5 constructs (Flotte et al, Wang et al, respectively). Therefore, there is reason to believe that the construct of Srivasta necessarily and inherently meets these claim limitations, even though Srivasta did not measure transcription activity relative to a wild-type AAV ITR. Therefore the reference construct reasonably meets the limitations of claims 1, 3, 8, 25, 27, 28, 30 and 34. Claim 9 requires "a transcriptionally active element of an APP promoter and a transcription initiator sequence; since both the B6 fragment and the APP promoter (in applicants SEQ ID no. 7) contain a TATATA sequence and a transcription initiation sequence about 30 nucleotides downstream, the B6 promoter fragment is seen as containing a transcriptionally active element of an APP promoter and a transcription initiator sequence in a segment less than about 70 nt, as required by claims 9 and 10, and further meets the limitations of claims 23 and 24.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 25-27 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al 5,587,308. Carter et al teaches promoter activity in AAV ITR, in a fragment of 145 bp. This differs from the claimed invention in that Carter et al teaches a wild-type ITR, not one with at least a two-fold increase in transcriptional activity. However, Carter et al teaches several elements of the ITR which resemble known promoter elements, and explicitly suggests modification of the ITR to modulate the transcriptional activity through standard mutagenesis techniques. Therefore, at least a two-fold improvement in transcriptional activity achieved by mutagenesis within the 145-bp ITR is seen as obvious, in view of the explicit suggestion by Carter et al.

Claims 31-33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srivasta as applied to claims 1, 3, 8-10, 23, 24, 25, 27, 28, 30, and 34 above, and further in view of Flotte et al 5,658,776 and Allen WO96/17947. These claims require stable integration of the AAV ITR polynucleotide, rep, and/or cap in a mammalian cell. Flotte et al teaches advantages of a packaging cell line with stably integrated AAV vector. Allen teaches advantages of a packaging cell line with stably integrated rep and cap genes. It would have been within the ordinary skill of

the art to further modify the teachings of Srivasta to produce a packaging cell line with any or all of these integrated materials, to achieve the advantages taught by the secondary references. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is (703) 308-2926. The examiner can normally be reached on Monday -Thursday and alternate Fridays from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is now (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 30, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600